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Table of Contents

Schedule at a Glance	Pages 4-8
Speaker Bios (Alpha by Surname)	Pages 9 - 27
Poster Index and Links	Pages 28-34
Poster Abstracts	Pages 35-128
Short Talk Index and Links	Page 129
Short Talk Abstracts	Pages 130-137

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Biohybrid Platform for Electrical Stimulation to Promote Insulin Secretion of Beta Cells

J. Kim, U. Yong, Y. Cho, D. Kim, and J. Jang

***Abstract*—Islet transplantation, a promising treatment for type 1 diabetes mellitus, has not yet been a golden standard due to the lack of donor islets and their low therapeutic efficacy. The electrical stimulation (ES) induces calcium ion influx triggering the insulin granule exocytosis, facilitating sufficient glycemic control with fewer islets. A system for uniform and nontoxic ES for 3D tissue construct is essential for reliable insulin secretion. Here, we fabricated a biohybrid platform with the integrated electrode and exerted ES on beta cells to verify upregulated insulin secretion. Increased therapeutic efficacy of islets would alleviate the lack of donor islets.**

***Clinical Relevance*— The ability to promote insulin secretion lessens essential number of islet equivalent for transplantation.**

I. INTRODUCTION

The beta cell plays a crucial role in controlling blood glucose level through insulin secretion. Glucose stimulation to beta cell results in membrane depolarization, inducing calcium influx and insulin secretion. Liebman *et al.* demonstrated that exposure to the electrical field ~3V/cm can increase intracellular calcium level and calcium spiking activity and enhance insulin secretion [1].

3D cell culture platform is a promising method to investigate cell behavior owing to its ability to recapitulate the microenvironment of tissue. To exert ES on the tissue, electrodes can be integrated into the platform. For ES without damage to tissue, conductive and biocompatible composite ink was fabricated by integrating carbon nanomaterials into biocompatible polymers. Asulin *et al.* showed that a complex biohybrid platform constructed by 3D printing composite ink was capable of applying ES to cardiac cell monolayer [2].

In this work, a biohybrid platform is fabricated for 3D pancreatic tissue. The electrode with large surface area was 3D printed by composite ink with carbon nanomaterials for uniform and harmless ES. Intracellular calcium concentration and insulin secretion are evaluated with ES.

II. METHODS

To 3D print the biohybrid platform, conductive ink was formulated by blending 25 wt% of carbon black with poly (ethylene-vinyl acetate) (PEVA). Polymer well structure and electrode were constructed using PEVA and conductive ink respectively. The electrode was passivated by pouring polydimethylsiloxane. A bioink prepared by mixing pancreas decellularized extracellular matrix with MIN6m9 was then injected into the platform.

Arduino nano and H-bridge circuit was used to control a biphasic pulse. The tissues were stained using LIVE/DEAD Viability/Cytotoxicity Kit. Glucose-stimulated insulin secretion (GSIS) was quantified using insulin ELISA kit. The calcium transients were measured with Fluo-4 AM.

III. RESULTS

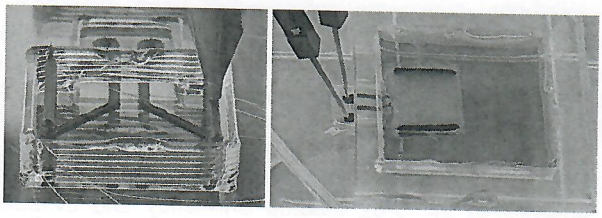

Figure 1. Fabrication process and final structure of biohybrid platform

The equivalent circuit of the system was constructed through electrochemical impedance spectroscopy. The exact electrical field was calculated through the circuit.

The tissue was subjected to ES after the stabilization of cells. The cells showed high viability with the presence of carbon black electrode and the ES. High capacitance of the electrode minimized the faradaic reaction in the media. The tissue exhibited higher intracellular calcium ion concentration compared to the tissue without external ES. The result corresponded with the high insulin secretion evaluated with GSIS. The properties of electrical stimulation (e.g., electric field, frequency, and pulse width) were optimized by cell viability and the level of insulin secretion.

IV. DISCUSSION & CONCLUSION

The promoted insulin secretion through intracellular calcium influx induced by ES was demonstrated. High versatility of additive manufacturing potentiates further usage for transplantation with wireless stimulation.

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J. Kim is with the Pohang University of Science and Technology, phone: +82 10-2928-0881 e-mail: kjihwan@postech.ac.kr).

None.References

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